Author’s response to reviews

Title: Encapsulating peritoneal sclerosis in a patient after allogeneic hematopoietic stem cell transplantation

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Author’s response to reviews:

Responses to the Comments

We would like to thank all reviewers for their careful reviews and useful suggestions. We very much appreciate their advice. The comments were all highly valuable and helped us revise and improve our manuscript. In addition, they have helped highlight the significance of our research. Our responses to all comments from the editor and reviewers are included below.

We hope this revision process allays all concerns related to the original manuscript.

Technical Comments:

1) Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file. Please remove the figure numbers (Figure 1, Figure 2, Figure 3) from the graphic files.

Thank you for the comments. We revised the figure graphic files without the figure numbers and have included figure titles and legends in the manuscript file.
We replaced Figures 1-3.

Comments from Simon Harrison (Reviewer 1):

This is an interesting case that is quite well written except for a few typographical and grammatical errors which should be proof read by and person with English as a first language. Some further details of the case would be useful

Thank you very much for this comment. We appreciate your spending time to review our manuscript. We had submitted the original manuscript after English proofreading, but it still contained some grammatical errors. Thus, we had the revised manuscript proofread again to correct the English before this re-submission.

<Added file>

We added a file certifying that the manuscript has been proofread.

page 6 what was the details of HLA matching of the two transplants and the timing of engraftment should be detailed.

Thank you for this comment. We added details of the HLA matching and information about neutrophil engraftment for the first and second HSCTs.

<Revised>

Line 91-93, Page 6

The patient received allogeneic HSCT using peripheral blood from a human leukocyte antigen (HLA) 6/6 matched sibling one month after hospitalization, with a conditioning regimen of cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy).

Line 93-95, Page 6

Neutrophil engraftment was achieved 21 days after the first HSCT. However, recurrence of MDS was confirmed 91 days after HSCT.

Line 96-99, Page 6

Four months after the initial HSCT, he received a second HSCT using HLA 4/6 bidirectional mismatched single unit cord blood with a conditioning regimen of fludarabine (150 mg/m2),
melphalan (80 mg/m²), and busulfan (12.8 mg/kg). GVHD prophylaxis consisted of tacrolimus and mycophenolate mofetil.

Line 99-100, Page 6

He achieved neutrophil engraftment at 15 days after the second HSCT.

Page 7 was the presumed engraftment syndrome treated with steroids?

Thank you for this comment. The patient was not administered any systemic steroid or additional immunosuppressive agents for engraftment syndrome because he had no organ dysfunctions and had a high risk of disease. His symptoms, other than ascites and pleural effusion, were improved after observation. To make the process of treatment of engraft syndrome clear, we added the following sentences.

<Revised>

Lines 104-107, Page 7

Initially, this was thought to be due to the engraftment syndrome because he presented with persistent fever without liver and kidney dysfunction. No additional immunosuppressive treatment was administered because he had no organ dysfunctions and had a high risk of disease.

Was the ascites and liver dysfunction persistent for the whole time up until the ascetic tap was performed?

Thank you for this comment. We apologize for the unclear sentences. The patient had no liver dysfunction. He had persistent ascites and pleural effusion for the entire time up until the ascetic tap was performed, as you point out. Accordingly, we revised the sentence to clarify that the patient had no liver dysfunction and his ascites was sustained.

<Added>

Lines 107-108, Page 7

His symptoms, other than ascites and pleural effusion, were improved after observation.
Ten months after the second HSCT, ascites inspection was performed because ascites and pleural effusion were sustained since the symptoms appeared.

I assume that the BO was treated, with what?, and that is why the serositis improved?

Thank you for this comment and suggestion. We treated the BO with clarithromycin and inhaled steroids. However, the patient did not receive any systemic corticosteroid. It is unclear why the serositis improved only with supportive therapy such as diuretics. Considering that some patients with GVHD improve without any treatment, we believe that it may be also possible for cGVHD-associated serositis to improve over time. We revised the manuscript to clarify that the patient had not been treated with a systemic corticosteroid before he was diagnosed with EPS.

He was treated with clarithromycin and inhaled steroids but without a systemic corticosteroid.

His serositis was also considered to be a cGVHD-related condition. His ascites decreased gradually and disappeared at one year after the second HSCT without a systemic corticosteroid or other immunosuppressive agents.

Discussion, given that serositis in general is unusual I would have expected some discussion about the treatment, etiology and outcomes of this before a detailed discussion of peritoneal sclerosis

Thank you for this comment and suggestion. We added the background, etiology, general treatment, and outcomes of serositis. EPS is also an unusual complication in non-PD patients. Thus, we added information on the background, etiology, treatment, and outcomes of EPS.
Serositis is recognized as inflammation of any of the serosal linings of the body. In a non-transplant setting, serosal inflammation can be caused by a variety of factors including infection, autoimmune disease, and malignant disease [2].

The incidence of EPS was 0.7-3.3 % in PD patients, and increased as the duration of PD was extended [10]. The exact etiology of EPS in non-PD patients was unclear, but some risk factors were reported. Chronic inflammation and its associated ascites retention may also cause EPS in non-PD patients; for example, tuberculous peritonitis and autoimmune disease were reported [4].

Regarding treatment and outcomes, immunosuppressive therapy, such as corticosteroids, was reported to be effective and the prognosis was good with a median survival of 105 months [2, 7-9].

Although the pathophysiology of EPS is also not fully understood, a two-hit theory is generally accepted [3].

Reference 10 was added.

Comments from Simon J Davies (Reviewer 2):
This is an very interesting case report - which is well presented.
I agree with the patient's diagnosis.

Provides some insight into the mechanisms of EPS

Thank you very much for this comment. We appreciate your spending time to review our manuscript. We totally agree with your suggestion. We added additional insights into the mechanisms of EPS in the Discussion section.

Minor comments.

Abstract conclusion: "Our case suggests that EPS may be complicated in patients with cGVHD associated serositis" - should read "EPS may complicate patients with cGVHD associated serositis"

Thank you for the comment. We revised this sentence.

<Revised>

Lines 58-59, Page 4

Our case suggests that EPS may complicate patients with cGVHD-associated serositis.

Given the suggestion that the inflammatory serositis led to the subsequent development of fibrosis and the development of EPS, it would be nice to mention more recent research in PD patients suggesting that intraperitoneal inflammation is very variable in PD, but does seem to predispose to EPS later e.g.


Thank you for these comments. They have helped us improve our manuscript. The manuscript you mentioned reported that an inflamed peritoneal membrane during PD was involved in the
subsequent development of EPS by inducing fibrosis in PD patients. In addition, another study reported that interleukin-6, which is associated with graft-versus-host disease and the development of EPS, drives fibrosis. So, we hypothesized that patients who developed cGVHD-associated serositis had chronic persistent inflammation in the peritoneal membrane. Then, this inflammation induced fibrosis of the peritoneal membrane, contributing to the development of EPS.

<Added>
Lines 166-168, Page 10

In addition, recent data suggested that an inflamed peritoneal membrane during PD was involved in the subsequent development of EPS by inducing fibrosis in PD patients [13, 14].

<Revised>
Lines 178-180, Page 11

Probably, the first hit (mesothelial disruption) occurred as a result of cGVHD-associated peritoneal inflammation, and the chronic persistent inflammation in the peritoneal membrane induced fibrosis.

<Added>
Lines 266-272, Page 17

References 13-14.

Lastly, we would like to thank all of you once again for your time to review our revised manuscript. We are looking forward to receiving your response.

Sincerely yours,

Yoshimitsu Shimomura, MD